IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

ALZA CORPORATION,

Plaintiff,

v. **CIVIL ACTION NO. 1:03CV61**
(Judge Keeley)

MYLAN LABORATORIES, INC. and
MYLAN PHARMACEUTICALS, INC.,

Defendants.

POST-TRIAL MEMORANDUM OPINION AND ORDER

This is a patent infringement suit involving a pharmaceutical invention disclosed by U.S. Patent No. 6,124,355 (issued Sept. 26, 2000) ("the '355 patent"). The plaintiff, Alza Corporation ("Alza"), holds title to the '355 patent. The defendants in this case are Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc. (collectively "Mylan").

Mylan committed acts of infringement by filing two Abbreviated New Drug Applications ("ANDAs") (Nos. 76-644 & 76-703) with the Food and Drug Administration ("FDA"), seeking permission to manufacture and distribute a generic version of an oxybutynin chloride extended-release tablet in 10 mg and 5 mg dosage forms, respectively. 35 U.S.C. § 271(e)(2). The ANDAs included a so-called "Paragraph IV" certification, which asserted that Mylan's products would not infringe the '355 patent and that the '355 patent is otherwise invalid. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

As statutorily required, Mylan notified Alza of its ANDA filings. See id. §§ 355(j)(2)(B)(i)-(ii). Consequently, Alza filed this infringement action on May 2, 2003.[1]

On December 7, 2004, the Court construed the disputed claims "according to [their] plain meaning and the parties' stipulated definitions" and denied Mylan's motions for summary judgment. Alza Corp. v. Mylan Labs., 349 F. Supp. 2d 1002, 1021 (N.D. W. Va. 2004). The Court subsequently held a ten day bench trial, which concluded on April 18, 2005. Thereafter, the parties filed extensive post-trial briefs.

Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, the Court now states its findings of fact and conclusions of law.[2] As discussed below, the Court concludes that Alza failed to meet its burden of proof with respect to its infringement claim and that the '355 is invalid as anticipated and obvious.

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[1] After Mylan submitted its second ANDA (No. 76-703), Alza filed another suit on June 26, 2003. The Court consolidated the cases by Order entered July 22, 2003 (dkt. no. 26).

[2] The substance of any statement shall govern whether it is treated as a finding of fact or conclusion of law.

I. BACKGROUND

Claims 1, 2, 3, 11, 13 and 14 of the '355 patent are the subjects of dispute in the case at bar. These product and method claims disclose a sustained-release (or extended-release) version of oxybutynin, a drug used for the treatment of urinary incontinence since the 1970s. (J. Stip. ¶ 34.) Before the invention of its sustained-release formulation, oxybutynin was administered two to four times a day to patients. '355 patent, col. 1:63-65. In contrast, the sustained-release formulation can be administered once a day because it delivers oxybutynin at a controlled rate over a 24 hour period. See id. at figs. 1 & 2.

Each asserted claim of the '355 patent recites a range of percentage or milligram amounts of oxybutynin that will be released within certain time intervals. In its claim construction, the Court determined that these ranges represent *in vivo* release rates, i.e., drug release in a human body. Alza, 349 F. Supp. 2d at 1019. The Court also construed the asserted claims to encompass osmotic[3]

[3] The tablet dosage form of Ditropan XL, the commercial embodiment of the '355 patent, utilizes an "OROS" (oral osmotic) system. This "platform technology" employs a bilayer push/pull osmotic pump delivery mechanism. An OROS tablet absorbs fluid through its semipermeable wall, causing one of its internal layers to expand. About two hours after ingestion, the expanded layer pushes out amounts of drug through a microscopic hole in the opposite end of the tablet.

and non-osmotic[4] dosage forms. See id. at 1010-11.

Mylan's ANDA product (or the "accused product") is a sustained-release oxybutynin formulation. Alza contends that the accused product releases drug within the claimed ranges of the '355 patent and thus infringes. Mylan denies infringement and affirmatively asserts several invalidity defenses, including inherent and express anticipation, inadequate written description, non-enablement and obviousness.

II. INFRINGEMENT

As the patentee, Alza bears the burden to show by a preponderance of the evidence that Mylan's product infringes the asserted claims of the '355 patent. Laitram Corp. v. Rexnord, Inc., 939 F.2d 1533, 1535 (Fed. Cir. 1991). "The infringement inquiry is a two-step process. [A] court construes the disputed claim terms and then compares the properly construed claims to the accused device." Metabolite Labs, Inc. v. Competitive Technologies, Inc., 370 F.3d 1354, 1360 (Fed. Cir. 2004) (citation omitted). "To literally infringe, the accused [product] must contain every limitation of the asserted claim." Texas Instruments Inc. v. Cypress Semiconductor Corp., 90 F.3d 1558, 1563 (Fed. Cir.

[4] Mylan's accused product uses a non-osmotic, enteric-coated polymer matrix dosage form that swells once ingested and releases drug through diffusion and erosion.

1996) (citation omitted). Furthermore, "it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent." Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1423 (Fed. Cir. 1994) (citing Martin v. Barber, 755 F.2d 1564, 1567 (Fed. Cir. 1985)); see also Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989) ("The scope of a patent's claims determines what infringes the patent[.]") (quotation omitted) .

In the case at bar, Mylan does not dispute that its accused product is a sustained-release oxybutynin formulation for oral administration to a patient containing a therapeutic dose of oxybutynin for treating incontinence. Therefore, Alza must prove that Mylan's 5 mg and 10 mg products satisfy each of the *in vivo* drug release limitations of the disputed claims. At trial, Alza did not elicit any scientific or testimonial evidence that establishes precise, numerical *in vivo* release rates for Mylan's accused product. Therefore, its infringement argument marshals evidence of (1) bioequivalence data from Mylan's accused product and Ditropan XL, and (2) *in vitro* testing of both drugs to estimate these release rates.

1. Bioequivalence Data Comparison

The first prong of Alza's infringement argument utilizes the results of Mylan's oxybutynin bioequivalence study,[5] which compared the mean plasma concentrations of oxybutynin in the blood of subjects taking Ditropan XL and Mylan's accused product under fasted conditions. (See, e.g., DX 1581.) Alza maintains that these two sets of data "closely match" and demonstrate an "*in vivo* relationship between Ditropan XL and [the accused product] blood levels that is achieved only by infringement."

In asserting that Mylan's bioequivalence data demonstrates infringement, Alza presupposes that *in vivo* release rates of different dosage forms are equivalent, inasmuch as their plasma concentration levels are equivalent. The evidence, however, fails to support this critical postulate. Indeed, undisputed trial testimony indicates that bioequivalent drugs do not necessarily share the same *in vivo* or *in vitro* release rates. (Amidon Tr. at 976; Wargo Tr. at 1303-04.) Moreover, in its opening post-trial memorandum, Alza admits that "[b]ioequivalence data shows blood levels of drug, . . . not release rates in the gastrointestinal

[5] To obtain approval for its ANDA, a generic drug manufacturer such as Mylan must submit "data demonstrating the generic product's bioequivalence with the previously approved drug." Mylan Pharms., Inc. v. Thompson, 268 F.3d 1323, 1326 (Fed. Cir. 2002) (citing 21 U.S.C. § 355(j)(2)(A)).

tract. Accordingly, it is necessary to extrapolate backwards to derive useful information about release of the product." (Alza Post Trial Br. at 24) (emphasis in original).

Alza nonetheless argues that "*in vivo* bioequivalence data can be used to understand [the accused product's] *in vivo* release rate." (Id. at 25.) In this vein, it relies heavily on the testimony of Mylan's expert, Dr. Gordon Amidon. Alza maintains that, "as Dr. Amidon explained, the high permeability of oxybutynin means there should be almost an equivalence between release in the GI tract and the appearance in the blood." (Id.) (citing Amidon Tr. at 1109-11). Alza also quotes the following excerpt from Dr. Amidon's testimony:

> Q. So the amount of drug that actually shows up in the blood is not the same as what is released in the GI tract, is that your-
>
> A. Correct.
>
> 1. Q. But the profile of the amount that shows up in the blood would match with the profile of the amount that shows up, that is released; is that true?
>
> A. Correct, yes.

(Amidon Tr. at 917-18.) The testimony cited by Alza confirms the obvious relationship between drug plasma levels and *in vivo* release rates. It does not, however, provide any objective and

quantitative estimate of the accused product's *in vivo* release rates vis-à-vis the claimed release rates in the '355 patent.

In Alza's bioequivalence data analysis, the only "direct" evidence proffered to show the accused product's *in vivo* release rates is an excerpt from Dr. Amidon's testimony during cross examination. (Amidon Tr. at 1174-76.) To introduce this reference, Alza states that, "[a]s discussed with Dr. Amidon, [the accused product's *in vivo*] release follows line A on the curve [illustrated on PX 611]." (Br. at 34.) The identified exhibit, PX 611, graphically compares the results of *in vitro* dissolution tests on Ditropan XL and the accused product. Not surprisingly, "line A on the curve," which was drawn on the exhibit by Alza's counsel, neatly falls within the claimed release ranges of the '355 patent. (See PX 611.) As Mylan notes, however, Dr. Amidon rejected the very conclusion that Alza attributed to him with respect to the meaning of line A:

> Q. Okay. So line A would be your best estimate of the *in vivo* release characteristic--excuse me, line A would be your best estimate of *in vitro* test results that would be predictive of Mylan's *in vivo* performance based upon your analysis of all of the data we talked about today, right?
>
> A. No.
>
> Q. I'm sorry?
>
> A. No.

(Amidon Tr. at 1176.)

Otherwise, no expert endorsed Alza's subjective comparison of blood plasma levels with *in vivo* release rates. Therefore, considering the evidence elicited at trial, the Court finds that the bioequivalence data alone offers no reliable basis to determine whether Mylan's accused product infringes and concludes that Alza has not met its burden to prove infringement using this data.

2. In Vitro Test Results

Alternatively, Alza contends that certain *in vitro* tests on the accused product demonstrate infringement. Initially, it relies on *in vitro* dissolution tests that Mylan submitted to the FDA to support its contention. (JX 197 at MYLAN 55511; JX 230 at MYLAN 65522-523.) These tests utilized "apparatus number 3," a reciprocating cylinder that churns the dosage form tablet up and down in a test tube. (Snyder Tr. at 783.) For Mylan's product, the apparatus operated at 25 dips per minute ("dpm") for a 24 hour period. The tablet was immersed in a solution of 1.2 pH for the first two hours of the test, then placed in a solution of 6.8 pH for the remaining 22 hours of the test. (Snyder Tr. at 819.) The amount of drug dosage released was measured over the 24 hour span.

Based on the reported data from the apparatus 3 dissolution test, Alza's expert, Dr. Nicholas Peppas, interpolated a 14 hour time point (Tr. at 288-89), and graphed the cumulative amount of

dose release over time for Mylan's 5mg and 10mg products. (PX 641.) These linear graphs of the accused products' *in vitro* release rates closely track the upper end of the claimed release ranges in the '355 patent. Alza, therefore, asserts that Mylan's FDA testing alone establishes infringement.

As further evidence of infringement, Alza offers the results of commissioned *in vitro* tests of the accused product conducted by Dr. Anthony Lowman. Dr. Lowman tested the Mylan tablets using apparatuses 1 (basket) and 2 (paddle) at a speed of 100 rpm, a commonly accepted speed for basket and paddle testing of controlled release formulations. (Lowman Tr. at 590, 596-97; JX 86, at 4.) He placed the tablets in a solution of pH 1.2 for the first 2 hours of testing (simulating gastric fluid), then transferred the tablets to a solution of pH 6.8 for the remaining 22 hours (simulating intestinal fluid). (Lowman Tr. at 594-95.) Dr. Lowman's dissolution test results indicate that the *in vitro* dissolution rates of Mylan's product fall within the *in vivo* release ranges claimed by the '355 patent. (See PX 632.) Alza asserts that these results demonstrate literal infringement.

Relying particularly on the undisputed testimony of Dr. Amidon, who has served on the Biopharmaceutics Expert Committee of the United States Pharmacopoeia ("USP") for the past ten years, Mylan contends that Alza's *in vitro* testing evidence is

insufficient to show *in vivo* release within the claimed ranges. (Amidon Tr. at 901.) Dr. Amidon explained that USP "dissolution procedures and methodologies are not designed to reflect the *in vivo* dissolution process." (Id. at 902.)[6] He further stated that, "if there is variability in the *in vitro* dissolution conditions or results," *in vivo* studies must be performed to determine the best correlation between the *in vitro* dissolution methodology and *in vivo* release rates. (Id. at 911-12, 1219.)

Similarly, the deposition testimony of Dr. Barr, Alza's expert, indicated that to establish *in vivo* release rates in an FDA submission it would be "simply unacceptable" to rely solely on a drug's *in vitro* dissolution profile without correlating *in vivo* results. (Tr. at 386-87; accord DX 403, at 1602 ("Some [*in vitro* release] tests attempt to simulate conditions *in vivo*, but as it has been pointed out the results of such tests are meaningless

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[6] Notably, the evidence indicates that the *in vivo* release rate of Ditropan XL differs from its *in vitro* release rate. The experts for both parties agreed that Ditropan XL *in vitro* release rates correlated with its *in vivo* release rates. (See, e.g., Amidon Tr. at 1110; Peppas Tr. at 299-300.) Correlation, however, does not necessarily constitute equivalence. Indeed, a study of the *in vitro-in vivo* correlation (or "IVIVC") of OROS oxbyutin (i.e., Ditropan XL) reported that the *in vitro* release rates of that drug are not equal to its *in vivo* release rates. (JX 89, at 711) (noting a "severe misfit" between the *in vitro* data and the *in vivo* data). Therefore, "to address this apparent lack of IVIVC," the study's authors "us[ed] a relatively simple form of systematic deviation from the *in vitro* release." Id. Dr. Amidon testified that the study indicates that the *in vitro* dissolution rates were faster than the *in vivo* release rates. (Tr. at 1183-84.)

unless correlated with quantitative *in vivo* measurements, even though they are valuable for manufacturing control purposes.")).

It is undisputed that the results of *in vitro* dissolution tests of Mylan's accused products differed "radically" depending on the choice of test apparatus, pH of testing medium and agitation speed. (Lowman Tr. at 713; see Amidon Tr. at 1258.) Therefore, *in vivo* studies, such as intubation or gamma scinitgraphy, are required to most accurately determine the correlation between the accused products' *in vitro* dissolution and *in vivo* release rates. (Lowman Tr. at 700-01; Amidon Tr. at 918-19.) In this case, however, no such studies were performed. Moreover, Dr. Lowman admitted he did not determine which dissolution test conditions best correlated with *in vivo* performance. (Lowman Tr. at 713-14.)

In the absence of any direct *in vivo* testing of Mylan's product, a numeric deconvolution analysis of blood plasma data offers the next best means for determining *in vivo* release rates. (Amidon Tr. at 919-20.) In its pretrial memorandum, Alza represented that it would offer a "deconvolution" analysis through Dr. Barr to establish that, based upon Mylan's bioequivalence data, the "accused products deliver oxybutynin into the GI tract of patients within the claimed ranges of the '355 patent." (Pl.'s Pre-Tr. Memo. at 30.) Nonetheless, Alza did not call Dr. Barr to

testify at trial, and presented no other expert testimony regarding a deconvolution analysis of the accused product.[7]

Alza cannot rely exclusively on *in vitro* test results to prove infringement of *in vivo* release rates. See Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991) (holding that "the district court erred in accepting the *in vitro* data as support for claim containing what has been found to be an *in vivo* limitation"). Indeed, without reliable *in vivo* data comparing the release rates of the accused product against the claimed ranges of the '355 patent, there can be no finding of infringement--either literally or under the doctrine of equivalents. Therefore, Alza has failed to meet its burden of proof with respect to infringement.

III. INVALIDITY DEFENSES

The Court presumes an issued patent's validity. 35 U.S.C. § 282. Therefore, a defendant must establish invalidity by facts supported by clear and convincing evidence. E.g., Beckson Marine,

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[7] Through Dr. Amidon's testimony, Mylan did introduce a numeric deconvolution analysis of the clinical trial plasma data submitted by Mylan to the FDA. (Amidon Tr. at 920-26; DX 1827-1833.) This analysis represents the only trial evidence of the accused product's *in vivo* release rates and indicates that those release rates fall outside the claimed ranges of the '355 patent. (Amidon Tr. at 925-26.) The reliability of these results is suspect, however, because the deconvolution incorporated IV data from different patients in an independent study that showed high variability among patients. (Amidon Tr. at 1081-84; see JX 116.) Therefore, the Court finds that Mylan's deconvolution results carry little, if any, probative weight in the infringement analysis.

Inc. v. NFM, Inc., 292 F.3d 718, 725 (Fed. Cir. 2002). Here, Mylan challenges the validity of Alza's '355 patent on several grounds.

A. Doctrine of Inherent Anticipation - 1996 WO Publication (the '895 Patent)

Under the doctrine of inherent anticipation, "[a] patent application fails if it is filed more than one year after the invention was described in a written publication." 35 U.S.C. § 102(b); Affymetrix, Inc. v. PE Corp. (NY), 306 F. Supp. 2d 363, 369 (S.D.N.Y. 2004). This rule precludes inventors from recapturing claims whose subject matter has already been placed into the public domain by an enabling published disclosure. 35 U.S.C. 102(b); see also Tronzo v. Biomet, Inc., 156 F.3d 1154, 1158 (Fed. Cir. 1998); Lockwood v. Am. Airlines, 107 F.3d 1565, 1570 (Fed. Cir. 1997). The parties have stipulated that Alza published an "International Application" under International Publication No. WO9 96/37202 ("1996 WO Publication) that enables one of skill in the art to make and use a sustained-release oxybutynin formulation/dosage form that satisfies the time range and release rate claim limitations of the '355 patent.

In certain circumstances, however, a patent is entitled to receive the benefit of the filing date of a previously filed patent application. 35 U.S.C. § 120. Frequently, this occurs in circumstances where a party files a series of related patents or

continuation-in-part ("CIP") applications. Alza's '355 patent is the fourth in a series of such related patents. The 1996 WO Publication publishes the first patent application in this series, U.S. Patent No. 567,895 (issued Oct. 7, 1997) ("'895 Patent"), filed on May 22, 1995.[8] Subsequently, Alza filed three CIP applications, U.S. Patent No. 5,840,754 (issued Nov. 24, 1998) ("'754 patent"), filed on September 5, 1996, U.S. Patent No. 5,912,268 (issued June 15, 1999) ("'268 patent"), filed on February 26, 1997, and, finally, the '355 patent, filed on May 13, 1998.

Alza contends that the claims in its '355 patent are entitled to receive the benefit of its '895 patent's filing date. Mylan mounts a number of arguments opposing this asserted priority date, all of which fall under the umbrella of the doctrine of inherent anticipation.

1. Threshold Priority Issue

Under 35 U.S.C. § 120, a patent application benefits from the filing date of a previously-filed patent application if the requirements of paragraph one of 35 U.S.C. § 112 are met, and if the patent application is filed before the previous application "or

[8] Because the 1996 WO Publication is the foreign publication of the '895 patent, the stipulations regarding the 1996 WO Publication also apply to the '895 patent.

an application similarly entitled to the benefit of the filing date of the first application" has been patented.

When Alza filed its '355 patent application, its '754 and '268 patent applications were pending. The '355 patent, therefore, may claim the '895 patent's filing date if the '895 patent and one of Alza's co-pending applications meet the requirements of § 112. See Berman v. Housey, 291 F.3d 1345, 1347 (Fed. Cir. 2002) (according the inventor the benefit of the filing date of "one of [his] earlier co-pending applications") (emphasis added).[9]

2. Section 112

Section 112 requires that a specification

> contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Three separate requirements, thus, must be satisfied - (1) the "written description" requirement, (2) the "enablement" requirement

[9] Although the '754 application is identical to the '895 patent in all material respects, it does add language regarding reduced side effects in patients. That issue is irrelevant to the priority issues, here, however, and the Court therefore will focus its analysis on the '895 patent, noting, however, that its findings with regard to that patent apply equally to the '754 patent.

and (3) the "best mode" requirement. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 921 (Fed. Cir. 2004).

Alza and Mylan have stipulated that the 1996 WO Publication meets the enablement requirement. Satisfaction of the "best mode" requirement by the '895 patent also is not in dispute. Mylan claims, however, that none of the patents filed by Alza prior to the '355 patent satisfies the "written description" requirement with respect to (a) the 4, 8, 14 and 24 hour time intervals for measuring in vivo oxybutynin release, (b) the claimed ranges of oxybutynin allegedly released in vivo at those time intervals, or (c) any non-osmotic pump dosage form that would meet the in vivo release limitations in the claims.[10]

3. "Written Description" Requirement

The "written description" requirement is designed to put future inventors on notice of the existence and scope of an invention and to prevent inventors from claiming ownership over more than they rightfully invented. Accordingly, the description

[10] Citing Alza's failure to perform in vivo testing, Mylan contends Alza never proved at trial that, in 1995, it knew of the product's in vivo performance. In terms of validity, however, the burden is on Mylan, not Alza, to prove that Alza did not perform in vivo testing, and to prove that it would have been clear to one skilled in the art reading the '895 patent that the drug, when administered to a patient in vivo, would not satisfy the release rates and ranges as described in the '895 patent. In determining whether the written description requirement has been met, the court will not distinguish between in vivo and in vitro results.

must "reasonably convey" to one skilled in the art that the inventor possessed the claimed invention at the time of the filing date. See, e.g., Augustine Medical, Inc. v. Gaymar Indus., 181 F.3d 1291, 1302 (Fed. Cir. 1999); Vas-Cath, 935 F.2d at 1562-631; Rambus, Inc., v. Infineon Technologies AG, 330 F. Supp. 2d 679 (E.D. Va. 2004); Affymetrix, 306 F. Supp. 2d at 370. Whether a patent satisfies this requirement is "a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1330 (Fed. Cir. 2003) (quoting Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324 (Fed. Cir. 2002)); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (stating that the "the precedential value of cases in this area is extremely limited").

In determining whether a previously-filed application meets the "written description" requirement, a Court must consider that "[e]ntitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed . . . . Rather, a prior application must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." Lockwood, 107 F.3d at 1570; Tronzo, 156 F.3d at 1158.

Alza concedes that the '895 patent does not expressly describe a non-osmotic pump delivery system such as utilized by Mylan's accused product or the time intervals and release rates claimed in its '355 patent. Nevertheless, it argues that these characteristics are inherent in its parent patent.

A patent's specification may inherently contain a disclosure sufficient to meet the written description requirement if "the missing descriptive matter must necessarily be present in the parent application's specification such that one skilled in the art would recognize such a disclosure." Tronzo, 156 F.3d at 1159; see also Kennecott v. Kyocera, 835 F.2d 1419, 1422-23 (Fed. Cir. 1987). Mylan contends that Alza's claims in the '355 patent are not inherent in the '895 patent because they broaden the scope of that patent's claims. As the following discussion explains, the Court finds that the '895 patent does inherently describe the time intervals and release rates claimed in the '355 patent, but does not inherently describe Alza's claim to non-osmotic delivery forms.

a. Written Description of the Critical Time Intervals and Release Ranges

Alza and Mylan stipulate that "the 5 mg bilayer osmotic pump dosage form made in accordance with the teachings of Example 5 in the 1996 WO Publication inherently performs the function of releasing oxybutynin as required by the limitations in claims 1 and

2 of the '355 patent," and that "the 10 mg bilayer osmotic pump dosage form made in accordance with the teachings of Example 6 in the 1996 WO Publication inherently performs the function of releasing oxybutynin as required by the limitations in claim 3 of the '355 patent." Moreover, Alza's expert, Dr. Peppas, and Mylan's expert, Dr. Amidon, both agreed that one of ordinary skill in the art reading these examples would recognize the release curve of an osmotic pump system delivering oxybutynin at a zero rate of release. (Peppas Tr. at 305-08; Amidon Tr. 1040-41). At trial, both also testified that the time ranges and rates of release claimed in the '355 patent fall within the scope of that curve. (Peppas Tr. at 305-08; Amidon Tr. 1040-41, 1044-45, 1056).

Accordingly, their testimony supports a finding that the '895 patent meets the written description requirement of § 112 regarding the critical time intervals and release ranges because Alza's claims in the '355 patent to the 4, 8, 14 and 24 hour time intervals and precise amounts of oxybutynin released at those intervals actually place more restrictive limitations on its original claim. Thus, the broad osmotic pump release profile inherently described in the '895 patent includes the specific ranges claimed by Alza in its '355 patent.

Mylan argues that these stipulations and the expert testimony do not dispose of this issue because a written description cannot

be inherent unless it is supported by *all* of the examples in a patent. However, in a recent decision, the Federal Circuit recently upheld a specification in a patent for an improved method of maintaining the orientation and attitude of a satellite in space, even though the second modulating step was not expressly described in the patent and did not appear in all of its figures. Space Systems/Loral, Inc. v. Lockheed Martin Corp., 405 F.3d 985, 989 (Fed. Cir. 2005) (finding that "a person of ordinary skill in this field of science would locate the second step" in light of expert testimony that the invention would be looked at as a "whole system").

Consistent with the holding in Space Systems/Loral, Alza's examples in the '895 patent represent steps in a process. Dr. Peppas testified that examples 1-4 demonstrate how to prepare the sustained-release dosage form, and examples 5-7 represent the invention in its completed form. (Peppas Tr. at 252-54, 308-11). Moreover, Dr. Amidon concurred with this view on cross-examination:

> Q. Okay. Now, going back to the '895 patent, examples 1 to 4 are building blocks that cumulate to the first fully functional extended-release dosage form, which is shown in example 5; is that right?
>
> A. Yes, that is how I read the patent.
>
> Q. Okay. So, basically, you see example 1 as disclosing a

therapeutic layer, correct?

A. Yes.

Q. And example 2 and 3 as two different kinds of hydrogel layers.

A. Yes.

Q. And example 4 puts them together into a two-layer tablet; is that right?

A. Yes.

Q. And example 5 coats it and turns it into an osmotic dosage form; is that right?

A. Yes.

Q. Okay. So when you look at the patent, you understand and the examples 5 and 6 are additional osmotic dosage forms; is that right?

A. Yes.

Q. And so when you look at the patent, you understand that the inventor is pointing to examples 5, 6, and 7 as the preferred embodiments of their invention, correct?

A. Yes.

(Amidon Tr. at 1041-43).

Thus, a person of ordinary skill in the art would recognize that the examples in the '895 patent must be examined as a whole in order to fully appreciate the scope of the invention. Examples 1-4

are building blocks and examples 5 and 6 represent Alza's invention in its completed form. The parties' stipulations that Alza's claims to the 4, 8, 14 and 24 hour time intervals and the ranges of oxybutynin released at those time intervals are inherent in examples 5 and 6 prevent Mylan from proving by clear and convincing evidence that these claims do not meet § 112's written description requirement. Alza, therefore, is entitled to the '895 patent's priority date with regard to its release rate and time interval claims. As discussed below, however, it is not entitled to priority with regard to its claim to non-osmotic dosage forms.

b. Written Description and Non-Osmotic Pump Dosage Forms

Alza contends that the claims in its '895 patent encompass any delivery system that is capable of achieving its desired result, i.e., the controlled delivery of oxybutynin for 24 hours. Although "[a] claim need not be limited to a preferred embodiment," Gentry Gallery v. Berkline Corp., 134 F.3d 1473, 1479 (Fed. Cir. 1998) (citing Ethicon Endo-Surgery, Inc. v. United States Surgical Corp., 93 F.3d 1572, 1582 n.7 (Fed. Cir. 1993)), "the description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention." Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997). "The

disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002) (citing Eli Lilly, 119 F.3d at 1568).

Whether the written description in a patent satisfies this requirement is an extremely fact-specific inquiry. Amgen Inc., 314 F.3d at 1330. In Ethicon Endo-Surgery, for example, the holder of a patent for a linear cutter stapler that discharges staples and locks when empty "was free to draft claim[s] . . . broadly (within the limits imposed by the prior art) to exclude the lockout's exact location as a limitation of the claimed invention" because he "did not consider the precise location of the lockout to be an element of his invention." 93 F.3d at 1582, n.7. In Gentry, on the other hand, the court invalidated a claim in a sofa patent that the controls for reclining the sofa seats could be placed in various locations because, "when viewed in its entirety," the "original disclosure clearly identifie[d] the console as the only possible location for the controls . . ." 134 F.3d at 1479.

A careful review of the claims, examples and specifications in Alza's '895 patent reveals an invention whose objects are to "provide a novel dosage form manufactured as an osmotic device" and "to provide a dosage form manufactured as an osmotic dosage form." (JX 4, at 2:41-44). Although there are other objects used to

describe Alza's invention, the '895 patent specifically states that, while "various changes, modifications, substitutions and omission can be made without departing from the spirit of the invention. . . [,] the invention embraces those equivalents within the scope of the claims." (Id. at 6:40-42) The claims, however, specify a therapeutic composition, a bilayered tablet and a delivery device. (Id. at 6-7).

Thus, in a vein similar to the sofa patent's disclosure in Gentry, Alza's original disclosure in the '895 patent clearly identifies a specific osmotic pump delivery device and does not even mention other variations. (JX 4). Furthermore, at trial, Dr. Peppas devoted a significant amount of testimony to explaining that the '895 patent inherently describes the claims in the '355 patent because one of skill in the art reading the '895 patent would immediately recognize the release curve characteristic of an osmotic pump system with a zero order rate of release. (Peppas Tr. at 305-08). Indeed, he stated that a reader feeling uncertain about the release rate intended by the '895 patent could refer to Figure 9 of the '377 Wong Patent, which depicts the typical release curve expected from an osmotic device. (Id.)

Relying on all this, the Court finds that Alza's claim to non-osmotic pump dosage forms is not entitled to the priority date of

the '895 patent for failure to meet the "written description" requirement.

This finding, however, does not lead to the conclusion Mylan advocates that Alza's non-osmotic dosage form claim is inherently anticipated by the 1996 WO Publication and, therefore, is invalid. Mylan has not established by clear and convincing evidence that the 1996 WO Publication enables the use of a non-osmotic, polymer matrix system to deliver the dosage form. Indeed, Mylan contends that the '355 patent itself fails to enable the use of non-osmotic systems, pointing to Dr. Amidon's "unequivocal[]" testimony that "the '355 patent does not enable a technology other than the OROS [osmotic pump] delivery system . . . ." (Amidon Tr. at 938). Moreover, Mylan concedes that the '355 patent broadens the scope of the '895 patent's claims and contains language providing for the use of dosage "forms" instead of one "osmotic" dosage "form", and also fails to limit the invention to "a" delivery device. (JX 1). Such contentions prevent Mylan from meeting its burden of proving that Alza's '355 patent is inherently anticipated by the 1996 WO Publication.

B. Written Description and Enablement of Non-osmotic Dosage Forms - '355 Patent

Mylan next argues that, regardless of whether the '355 patent is inherently anticipated by the 1996 WO Publication, it is still invalid for failure to meet the "written description" and "enablement" requirements of § 112. These arguments are without merit.

1. Written Description

As stated in the Court's December 7, 2004 "Order Construing Claims and Denying Summary Judgment," the parties have stipulated that a "dosage form" is "a pharmaceutical preparation in which doses of medicine are included" and a "solid dosage form" is "a dosage form that is neither liquid nor gaseous."

> As used in the '355 Patent . . .the term "dosage form" comports with its broad stipulated definition. In the section entitled "Objects of the Invention," the patent qualifies the term in numerous ways: "sustained-release dosage form," "solid-oral dosage pharmaceutical form," "drug delivery dosage form," "controlled-release dosage form," and, most notably, "an osmotic dosage form." '355 Patent, cols. 2-3. The examples in the written description also indicate that the invention encompasses more than one dosage form. Moreover, the patent refers to both osmotic and non-osmotic dosage forms. Thus, in the examples cited by Mylan, the osmotic dosage form is merely a preferred embodiment . . .

Alza Corp. v. Mylan Labs., 349 F. Supp. 2d 1002, 1010 (N.D. W. Va. 2004).

The '355 patent only refers to "dosage form" or "dosage forms"; unlike the '895 patent, it makes limited use of the term "osmotic." (JX 1). It also claims "a method for treating incontinence" instead of claiming "a delivery device." (Id. at 12). Moreover, Dr. Amidon testified that skilled artisans would be aware of the different types of dosage forms encompassed by the genus of sustained-release dosage forms claimed by the '355 patent. (Amidon Tr. at 1051-52). Thus, while the words "non-osmotic" dosage form and "polymer matrix" are not expressly written in the patent, one of skill in the art reading the '355 patent would realize that the term "dosage form" includes a variety of known pharmaceutical preparations, including a non-osmotic polymer matrix delivery device.

2. Enablement

As noted earlier, to enable a claimed invention, a patent must provide a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, ¶ 1 (2000). "The purpose of this requirement is to ensure that 'the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.' Accordingly . . . the specification must provide sufficient teaching such that one

skilled in the art could make and use the full scope of the invention without undue experimentation." Warner-Lambert Co. v. Teva Pharms. United States, No. 04-1506, 2005 U.S. App. LEXIS 16880, *23-*24 (Fed. Cir. Aug. 11, 2005).

> [W]hether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." Some of these considerations, commonly referred to as "the Wands factors," include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Id. at *24-*26 (quoting In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988); see also Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that the Wands factors "are illustrative, not mandatory" and that what is relevant to an enablement determination depends upon the facts of the particular case).

At trial, both Dr. Peppas and Dr. Amidon acknowledged that many known non-osmotic systems, including a polymer matrix dosage form, existed so that one of ordinary skill could make and practice the limitations of the '355 patent based on the prior art. (Amidon Tr. at 1051-52; Peppas Tr. at 222, 530-31). Dr. Peppas further stated that this could be achieved without undue experimentation

and with a reasonable degree of predictability. (Peppas Tr. at 530-31).

Mylan's contention that it can prove lack of enablement by clear and convincing evidence is foreclosed by its assertion that Alza's 1996 WO Publication is an enabling disclosure that inherently anticipates the '355 patent's claims. Mylan, therefore, cannot meet its burden of proving the invalidity of the '355 patent for failure to meet the written description and enablement requirements of § 112.

C. Inventorship

Section 102(f) provides that "[a] person shall be entitled to a patent unless--he did not himself invent the subject matter sought to be patented. . . ." 35 U.S.C. § 102(f) (1994). "If failure to comply with section 102(f) is proven by clear and convincing evidence, the claims of a patent will be held invalid." Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1381 (Fed. Cir. 2000); Hess v. Advanced Cardiovascular Sys., Inc., 106 F.3d 976, 980 (Fed. Cir. 1997).

According to Mylan, Alza conceived and designed its invention before the named inventors became involved with the project. Specifically, Mylan claims that the named inventors did not perform the in vivo work contained in the '355 patent and that Alza is falsely giving them credit in an attempt to "piggy-back" this work,

which is not explicitly referenced in the original '895 application, onto its earlier applications. Other than presenting U.S. Patent No. US 2001/0009995 A1 (issued July 26, 2001), filed on March 7, 2001 by Drs. Gupta, Sathyan and Saks ("Gupta patent"), who are employees of Alza, and claiming that it contains in vivo work regarding the sustained-release of oxybutynin, Mylan offers little concrete evidence to support its inventorship theory.

Indeed, during trial Mylan offered no testimony from any of these "true inventors." Despite bearing the burden of proving that the named inventors were not responsible for the in vivo release profile recited in the claims of the '355 patent, it admonishes Alza for failing to bring Drs. Gupta, Sathyan or Saks to trial, and for failing to prove any "conception" of an actual in vivo drug release profile in a human patient by anyone other than Drs. Gupta, Sathyan and Saks prior to this date.

The most significant evidence marshaled by Mylan in favor of its theory is the deposition testimony of the named inventors of the '355 patent. Individually, each indicated he had no involvement in or knowledge of the in vivo performance of the claimed dosage form. None, however, identified Drs. Gupta, Sathyan or Saks as the true inventors, or as having contributed to the development of the invention. Moreover, "[w]hile an inventor's statements made during the course of litigation might in some circumstances justify a

court in concluding that the named inventor 'did not himself invent the subject matter sought to be patented,' it would require much stronger evidence that the named inventor was not the true inventor to justify a conclusion of clear and convincing evidence of invalidity." Solomon, 216 F.3d at 1381. The facts evinced by Mylan at trial, thus, do not prove by clear and convincing evidence that Alza did not name the true inventors in its '355 patent.

D. Anticipation

"A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim." EMI Group N. Am., Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1350 (Fed. Cir. 2001). "Anticipation is a question of fact." Merck & Co., Inc. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003).

Mylan contends that U.S. Patent Nos. 5,330,776 (issued July 19, 1994) ("the Morella patent" or "Morella"); 5,399,359 (issued Mar. 21, 1995) ("the Baichwal patent" or "Baichwal"); 5,082,668 (issued Jan. 21, 1992) ("the Wong patent" or "Wong"); and 5,532,278 (issued July 2, 1996) ("the Aberg patent" or "Aberg") each independently anticipates the '355 patent. (See JX 19; JX 18; JX 22; DX 1035.) Mylan also asserts that two prior art studies anticipate the method claims of the '355 patent.

1. Morella

Morella discloses a "sustained-release pharmaceutical composition including an active ingredient of high solubility in water." (JX 19, at 1:10-12.) In claim 2, the patent claims "genitourinary smooth muscle relaxants" as one of several types of active ingredients to use in the dosage form recited in claim 1. (Id. at 24:12-13.) Oxybutynin is specifically identified in the specification as one of two highly soluble genitourinary smooth muscle relaxants. (Id. at 5:29-32.) Morella further teaches that "the dissolution rate of the soluble drug at various pH's can be modified at will by altering the ratio of polymers." (Id. at 9:5-12.)

Relying on Dr. Amidon's testimony, Mylan asserts that Morella enables the manufacture of sustained-release drugs across a broad range of different release profiles--including those claimed in the '355 patent. (Amidon Tr. at 954-64.) Mylan also maintains that tests of formulations defined in Morella's claims 1 and 2 confirm anticipation of the '355 patent claims. (Amidon Tr. at 962-964; JX 55; DX 1403; JX 25.) Alza, on the other hand, argues that Morella cannot anticipate because it (1) does not teach whether oxybutynin can be absorbed in the colon, (2) does not discuss "many of the issues necessary to developing a controlled-release formulation", (3) dissuades a person of ordinary skill in the art from developing

an oxybutynin controlled release formulation, (4) does not identify a specific "therapeutically effective amount" of oxybutynin to be placed in the dosage form, and (5) is not enabled for oxybutynin.

The majority of Alza's contentions are unavailing. First, the '355 patent does not claim colonic absorption rates of oxybutynin; therefore, the extent of oxybutynin's absorption in the colon has no bearing on the anticipation analysis. Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1381 (Fed. Cir. 2003) ("An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more.")

Likewise, the "drug development issues" identified by Alza are irrelevant because they, too, are not included in the '355 patent claims. Furthermore, "the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001) (quotation omitted). Thus, the Court need not consider whether Morella implies that oxybutynin may not be a suitable candidate for a controlled release formulation.

A specified "therapeutically effective amount" of oxybutynin in Morella is also unnecessary to demonstrate anticipation. The '355 patent claims "[a] sustained-release oxybutynin formulation for oral administration to a patient comprising a therapeutic dose of . . . oxybutynin" that delivers certain percentages of the drug

at certain time intervals. (See, e.g., '355 patent at 17:21-30.) With respect to the asserted claims, only claim 12 identifies a specific amount of therapeutic dose to be used in claim 11, a method claim. Otherwise, according to the parties' stipulated definition, "therapeutic dose" means "a quantity of a drug that is useful in treating a particular disease or condition." (Joint Claim Construction Report at 3.) This definition reads broadly, encompassing drug quantities that are less than optimal but nonetheless useful for treatment. Therefore, the Court discerns no meaningful difference between the terms "therapeutically effective amount," as recited in Morella, and "therapeutic dose," as recited in the '355 patent.

The remaining issue raised by the parties is whether Morella enables the manufacture of an oxybutynin dosage form that reads on the claims of the '355 patent. See Bristol-Myers Squibb Co., 246 F.23 at 1379. The Court must "presume the enablement of unclaimed (and claimed) material in [an allegedly invalidating] prior art patent." Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1355 (Fed. Cir. 2003). The patentee can rebut this

presumption, however, by presenting "persuasive evidence of nonenablement."[11] Id.

To show nonenablement, Alza argues that only by undue experimentation was Mylan able to reformulate the Morella dosage form to deliver oxybutynin within the claimed ranges of the '355 patent. See Amgen, 314 F.3d at 1334 ("The enablement requirement . . . is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'") (citations omitted). In particular, Alza asserts that Mylan "made at least 29 formulations of the Morella dosage form" before producing a dosage form that fell within the claims of the '355 patent.

Nonetheless, Alza offers no corroborating evidence indicating that the Morella formulations constituted undue experimentation. To the contrary, both Dr. Peppas and Dr. Amidon agreed that the Morella formulations were within the bounds of routine experimentation for one skilled in the art. (Peppas Tr. at 510; Amidon Tr. 964.) Therefore, the Court finds that Alza fails to present persuasive evidence of nonenablement. Since Alza concedes that the Morella formulations produced a dosage form that fell

[11] Mylan erroneously asserts that Alza bears the burden of proving nonenablement by clear and convincing evidence, citing the Amgen decision. In Amgen, however, the Federal Circuit plainly does not impose such a high burden of proof on the patentee. 314 F.3d at 1355.

within the claims of the '355 patent (Pl.'s Post-Tr. Memo. at 43), the Court concludes that Morella anticipates the '355 patent.

2. Baichwal

The Baichwal patent teaches a 24 hour extended-release oral dosage form with 5 mg to 20 mg of oxybutynin chloride. (JX 18, at 2:38-44, 3:5-9.) These formulations implement an enteric-coated polymer matrix dosage form similar to Mylan's accused product. (See Amidon Tr. at 943-45.) Baichwal also teaches methods to achieve slower release rates by modifying the dosage forms. (Amidon Tr. at 941-43; JX 18, at 6:24-12:26.) The patent incorporates by reference prior Baichwal patents utilizing the same dosage form technology. (JX 18, at 1:44-51.)

The Patent and Trademark Office ("PTO") initially rejected the claims of the '355 patent as anticipated by Baichwal. (JX 3, at Ex. 7.) The Examiner reasoned that "since the materials taught in the prior art are similar to those of the ['355 patent], then the physical properties and activity of the composition would be similar to those of the instant claimed invention in the absence of factual evidence to the contrary." (Id.) Relying on the dissolution data presented in Baichwal, Alza responded by arguing that the dissolution rate claimed in the '355 patent is "significantly slower." (Id. at Ex. 9.) The Examiner agreed, and subsequently withdrew the anticipation rejection. (Id. at Ex. 10).

In light of the Examiner's consideration of Baichwal during the prosecution of the '355 patent, Mylan bears the additional burden "of overcoming the deference that is due to a qualified government agency presumed to have properly done its job . . . ." Am. Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir. 1984). To that end, Mylan focuses its attention on a Finnish drug named Cystrin CR, a 24 hour controlled release dosage form containing 10 mg of oxybutynin hydrochloride. (JX 104 at 1.) Although not prior art, Cystrin CR is directly relevant to the anticipation analysis in this case because formulations 1 and 2 of that drug are manufactured according to examples 3 and 4 in the Baichwal patent. (Amidon Tr. at 952-53.)

As the parties stipulated, deconvolutions of Cystrin CR blood concentration data demonstrate that, in the fasted state and the "one hour before breakfast state," Cystrin CR releases oxybutynin in vivo within the ranges claimed in the '355 patent. (Tr. at 1068-69; JX 101.) The parties also agreed that deconvolution of Cystrin CR blood data from the "two hours after breakfast state" and the "breakfast state" "show oxybutynin release that is significantly more rapid than the claimed ranges." (Tr. at 1069; see JX 101; PX 482.) Since the measured Cystrin CR formulations indisputably correspond to the Baichwal examples, Mylan contends that Baichwal anticipates.

To rebut Mylan's anticipation argument, Alza points out that Cystrin CR releases oxybutynin outside the claimed ranges under fed conditions and thus cannot establish Baichwal's inherent anticipation. Such an application of inherent anticipation law, however, is inconsistent with the correlative law of infringement and the evidence in the case. As a foundational patent law principle, "that which would literally infringe if later anticipates if earlier." Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001) (citation omitted). Alza's opening brief acknowledges that "conditional infringement" nonetheless confirms infringement:

> There is no doctrine excusing de minimus - or only "sometimes" - infringement. E.g., Suntiger, Inc. v. Scientific Research Funding Corp., 189 F.3d 1327 (Fed. Cir. 1999). If a product avoids infringement under some circumstances, "this has little bearing on whether [the product] will avoid infringement under other foreseeable operating conditions." Canon Computer Sys., Inc. v. Nu-Kote Int'l, Inc., 134 F.3d 1085, 1089 (Fed. Cir. 1998). A product either does, or does not, infringe the claims.

(Alza Post-Tr. Memo at 35-36.) Likewise, prior art either does, or does not, anticipate the claims of the '355 patent "under foreseeable operating conditions."

In the case at bar, the '355 patent claims are not limited to administration of sustained-release oxybutynin to patients in a

"fed state."[12] Based on the deconvolution data, Dr. Peppas, Alza's expert, also admitted that, Cystrin CR would infringe the '355 patent if sold in the United States. (Peppas Tr. at 352.) The Court, therefore, concludes that examples 3 and 4 of Baichwal anticipate the '355 patent and specifically finds that Mylan has overcome its heightened burden to show anticipation because the PTO did not compare any *in vivo* data before ratifying the novelty of the '355 patent claims.

3. Wong

The Wong patent discloses a bilayer osmotic pump dosage form (or "OROS system") that is used in the preferred embodiment of the '355 patent. (JX 22; Wong Tr. at 94?) Wong teaches that the OROS system can deliver any organic or inorganic drug over a 24 hour period. (JX 22 at 19:65-67; Peppas Tr. 354-55.) Indeed, the patent lists numerous compounds and drug types that can be delivered by the OROS system. (JX 22, at 19:49-21:20.) Moreover, figure 11 of the patent discloses release rates corresponding to the claimed '355 patent release rates. (Peppas Tr. at 490.)

Mylan contends that Wong anticipates by disclosing release rates within '355 patent ranges and identifying different

[12] Alza also suggests that Baichwal cannot anticipate because it does not teach zero-order release or a constant rate of release. These limitations, however, are not included in the claims and are, thus, irrelevant to the anticipation determination.

categories of drugs for use in the OROS system that include oxybutynin, such as anti-cholinergics, analgesics, muscle relaxants and urinary tract drugs. As Alza notes, however, the Wong patent does not specifically list oxybutynin for use in the OROS system.

"A prior art reference that discloses a genus still does not inherently disclose all species within that broad category." Metabolite Labs, 370 F.3d at 1367 (citing Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989)). The only exception to this rule is when the bare disclosure of the genus allows a person of ordinary skill in the art "to at once envisage" the species. In re Petering, 301 F.2d 676, 681 (C.C.P.A. 1962); see also Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001) ("[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited.") (citing Petering).

Here, Mylan elicited no evidence demonstrating that a person of ordinary skill in the art would "at once envisage" oxybutynin when reading the Wong patent. Instead, it improperly engages in hindsight analysis, relying on testimony from Dr. Amidon to establish that some of the compound categories listed in the Wong patent include oxybutynin. Dr. Amidon admitted, however, that he was not familiar with oxybutynin in the mid-1990s. (Amidon Tr. at 1033-34.)

Mylan also argues that Alza's listing of the Wong patent in the FDA "Orange Book" for Ditropan XL establishes that Wong anticipates. (JX 112.) The Orange Book listing for Ditropan XL includes six different patents (including the '355 patent) that "cover the formulation, composition, and/or method of use of" the drug. (Id.) Mylan does not offer any evidence or legal authority suggesting that the inclusion of the Wong patent in the listing is necessarily probative of anticipation. Therefore, the Court concludes that Mylan has failed to show by clear and convincing evidence that Wong anticipates the '355 patent.

4. Aberg

Aberg claims the administration of the S(-) enantiomer of oxybutynin to treat urinary incontinence. (DX 1035, at 6:48-66.) The patent states that the recited oxybutynin compounds "may also be administered by controlled release means and delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719 ["the '719 patent"], and PCT application WO92/20377, the disclosures of which are hereby incorporated by reference." (Id. at 4:19-26.) According to Mylan, the '719 patent contains a teaching showing the exact release rates as claimed in the '355 patent. (DX 1024.)

Because Mylan elicited no direct expert testimony on Aberg's alleged anticipatory character, its argument principally relies on

the cross-examination testimony of Dr. Peppas, Alza's expert. (Peppas Tr. at 469-74.) That testimony, however, does not clearly and convincingly show that the '719 patent (as incorporated by Aberg) teaches either drug release over 24 hours or *in vivo* release rates falling within the claimed ranges of the '355 patent. Accordingly, Mylan has not established that Aberg anticipates.

5. Method Claims

Finally, Mylan contends that the asserted method claims in the '355 patent are anticipated by two prior art publications that report the administration of multiple doses of immediate release oxybutynin to patients over the course of 24 hours. (DX 433; DX 453.) As Alza observes, however, the '355 patent claims a method of administering a single dose of an oxybutynin formulation with a controlled, *in vivo* delivery of the drug over 24 hours. (JX 1, at 18:8-27.) Therefore, the Court concludes that neither of Mylan's cited articles anticipates every limitation of the '355 patent method claims.

E. Obviousness

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). The obviousness inquiry is a

question of law that requires specific factual findings, including "the scope and content of the prior art, the level of ordinary skill in the field of the invention, the differences between the claimed invention and the prior art, and any objective evidence of non-obviousness . . . ." SIBIA Neurosciences v. Cadus Pharm. Corp., 225 F.3d 1349, 1355 (Fed. Cir. 2000) (citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

1. Level of Ordinary Skill in the Art

Whether the claimed invention is obvious must be evaluated from the perspective of a hypothetical person of ordinary skill in the art. Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985). This hypothetical person presumptively "thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." Id. In their post-trial memoranda, the parties do not directly dispute the level of ordinary skill in the art at the time of the '355 patent's filing. Thus, based on the testimony of Dr. Amidon and Dr. Peppas, the Court finds that a person of ordinary skill in the art has either an advanced degree in pharmacy, biology, chemistry or chemical engineering and has at least two years of experience with controlled-release drug technologies, or possesses a bachelor's degree in one (or more) of the same fields and has at least five

years of experience with controlled-release drug technologies. (Amidon Tr. at 979-80; Peppas Tr. at 317.)

2. The Prior Art and the Claimed Invention

"[T]he relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." Ruiz v. A.B. Chance Co., 234 F.3d 654, 664 (Fed. Cir. 2000) (citations omitted). The inspiration to combine prior art references must also offer a "reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988).

a. Motivation to Combine References

In the case at bar, ample evidence establishes a "reason, suggestion, or motivation" to combine prior art references to produce a 24 hour controlled release oxybutynin dosage form that reads on the claims of the '355 patent. Most notably, the Morella patent specifically identifies oxybutynin as a compound to use in a dosage form with release rates within the claimed ranges of the '355 patent. (JX 19, at 5:29-32.) Likewise, the Wong patent, especially when read in conjunction with Morella, would suggest the placement of oxybutynin (a commonly known "muscle relaxant" and "urinary tract drug") in an OROS system, thereby producing the preferred embodiment of the '355 patent.

The Baichwal patent, which already taught the 24 hour release of oxybutynin, also offers an independent suggestion to produce a oxybutynin dosage form with release rates falling within the '355 patent claims. Baichwal incorporates by reference the inventor's previous patents describing "controlled release oral solid dosage forms," including U.S. Patent No. 5,135,757 (issued Aug. 4, 1992) ("the '757 patent"). The '757 patent states that "it would be obvious to one skilled in the art that by varying [the ratio of medicament to hydrophillic material] and/or total weight of the tablet, etc., one can achieve different slow release profiles, and may extend the dissolution of some medicaments to about 24 hours." (DX 1801, at 9:8-20.)

Alza nonetheless argues that other references in the prior art would dissuade a skilled artisan from pursuing a 24 hour controlled release oxybutynin dosage form. A finding that a prior art reference "teaches away" from combining references can alone defeat an obviousness claim. Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000) (citing Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1579 (Fed. Cir. 1997)). "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the

applicant." Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (quotation omitted).

In support of this argument, Alza points to several characteristics of oxybutynin that purportedly teach away from using the drug in a 24 hour controlled release dosage form. It maintains that drugs that are highly metabolized and exhibit pH-dependent solubility, such as oxybutynin, are poor candidates for controlled delivery. (JX 116; Amidon Tr. at 1018-20; PX 467, at 17; PX 400, at 1490.) It also asserts that drugs with a half-life of 2 hours or less, which oxybutynin was believed to have, are poor candidates for controlled-release formulations. (JX 116, at 515; Amidon Tr. at 1022-23.)

In this case, prior art references did not discourage the pursuit of developing a 24 hour controlled release oxybutynin dosage form. First, Alza fails to identify prior art indicating that highly metabolized drugs are poor candidates for controlled delivery. Instead, it relies on testimony from Dr. Amidon regarding a slide he had used in his college course. (Amidon Tr. at 1018-20; PX 594.) Moreover, in marketing Ditropan XL, Alza touted oxybutynin as "an excellent candidate for controlled drug delivery" in part because it "undergoes extensive first-pass metabolism." (PX 157, at 25.)

Viewing the evidence as a whole, the Court concludes that oxybutynin's pH-dependent solubility and half life would not discourage the development of a controlled release version of the drug. With respect to oxybutynin's solubility, the article cited by Alza states that "[d]rugs with a very strong, pH-dependent solubility over the physiologic pH range of the GI tract may be poor candidates for oral sustained release products." (PX 467, at 17) (emphasis added). This moderately equivocal statement cannot be weighed in isolation from the numerous other factors that can influence a drug's suitability for controlled release formulations. (Amidon Tr. at 1015-16; Peppas Tr. at 218-21; see PX 467, at 16 - "Often it is necessary to consider various properties together . . . in order to determine the viability of a candidate drug for a sustained release product."). Moreover, the Baichwal patent clearly suggests that oxybutynin could be used in a controlled release dosage form, and notes that, at the time of the patent's issuance, no such oxybutynin formulation was commercially available. (E.g., JX 18, at 2:9-11, 1:25-31.)

Oxybutynin's half life, in particular, is a factor that could encourage a skilled artisan to pursue a once-a-day formulation. The prior art reported that the half life of oxybutynin was "about 2 hours." (JX 116, at 515.) As Dr. Amidon's class slide indicated, "[s]hort half-lives are preferred," although a half-life

less than 2 hours is less desirable because it "requires large amounts of drug" for a controlled release dosage form. (PX 594.) Indeed, Alza's product monograph for Ditropan XL confirms that oxybutynin's "short plasma half-life" is one of several factors that make the drug "an excellent candidate for controlled drug delivery." (PX 157, at 25.) Thus, the Court discounts Dr. Amidon's cross-examination testimony suggesting that drugs with an elimination half life of 2 hours or less are poor candidates for controlled release, particularly because counsel's question simultaneously inquired about drugs with half-lives of greater than 8 hours, which are "not desirable" for controlled release dosage forms. (Amidon Tr. at 1022-23; PX 594.)

In summary, the Court finds that the prior art provided sufficient motivation for a skilled artisan to develop a 24 hour controlled release dosage of oxybutynin.

b. Reasonable Expectation of Success

Alza also argues that a person of ordinary skill in the art had no reasonable expectation of success in producing a 24 hour controlled-release oxybutynin formulation. In particular, it emphasizes that oxybutynin's ability to absorb in the colon was unknown but necessary for successful controlled delivery. (See Amidon Tr. at 1002, 1032-34, 1037.) Mylan, however, asserts that

a skilled artisan would have reasonably expected oxybutynin to absorb in the colon.

As an initial matter, on a purely mechanical level, a skilled artisan would have a reasonable expectation of success of manufacturing a 24 hour controlled-release oxybutynin formulation within the limitations of the asserted patent claims. Indeed, once motivated to use oxybutynin, a person of ordinary skill in the art could apply the teachings of the Wong patent alone to produce a drug constituting the preferred embodiment of the '355 patent. (See Wong 111-18; Amidon Tr. at 966-69.)

With respect to the colonic absorption issue,[13] Mylan presented unrebutted and unimpeached evidence demonstrating that a person of ordinary skill in the art would reasonably expect oxybutynin to absorb in the colon. Dr. Chancellor, Alza's expert, conceded that oxybutynin was a "well-known highly lipophilic molecule" and that it was "published knowledge" prior to 1995 that lipophilic drugs are likely to be well absorbed in the colon. (Chancellor Tr. at 1551.) Dr. Amidon similarly testified that a skilled artisan would expect a "highly lipophilic drug" like

[13] The analysis of oxybutynin's colonic absorption overlaps the earlier discussion in this opinion of whether the prior art teaches away from a 24 hour controlled release oxybutynin formulation, and the later discussion of unexpected results. No matter where placed, the Court finds that the outcome would remain the same.

oxybutynin to absorb "well" and "rapidly" in the colon. (Amidon Tr. at 1898.)

In its post-trial reply memorandum, Alza argues that Mylan's focus on the lipophilicity of oxybutynin "trivializes the complicated science involved in once-a-day formulations." It subsequently quotes the following text from an article cited by Dr. Amidon:

> H216/44 (which is more lipophilic than metoprolol) was transported at a relatively slow rate across the monolayers. The reason for this is currently unknown, but may be related to the bulky chemical structure of this compound. Another lipophilic β-blocking agent, acebutolol, has also been reported to be absorbed at an unexpectedly slow rate across intestinal epithelium.

(DX 2002, Tab O, at 481.) Alza stresses that, when questioned about this text, Dr. Amidon's stated that "all lipophilic drugs do not have the same rate of absorption." (Amidon Tr. at 1965-66) (emphasis added). It also notes that human studies must be performed to determine whether a lipophilic molecule will be absorbed in the colon. Nonetheless, it proffers no evidence suggesting that a lipophilic drug's typical colonic absorption rate is either low or unknown.

At most, Alza establishes that a drug's high lipophilicity fails to guarantee optimal colonic absorption. The standard for obviousness, however, is much less restrictive. Therefore, the Court concludes that the weight of the evidence clearly and

convincingly establishes that a person of ordinary skill in the art in 1995 would reasonably expect oxybutynin to absorb in the colon. Accordingly, it finds that a skilled artisan would also have a reasonable expectation of success of producing a 24 hour oxybuytnin formulation meeting the claims of the '355 patent.

3. Secondary Considerations

Secondary considerations, also known as indicia of nonobviousness, "must be considered in determining obviousness." Ruiz, 234 F.3d at 667 (citations omitted). "Evidence of secondary considerations may often be the most probative and cogent evidence in the record." Stratoflex, 713 F.2d at 1538.

a. Commercial Success

> [T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art. When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention. If a patentee makes the requisite showing of nexus between commercial success and the patented invention, the burden shifts to the challenger to prove that the commercial success is instead due to other factors extraneous to the patented invention, such as advertising or superior workmanship.

J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997) (citing Richdel, Inc. v. Sunspool Corp., 714 F.2d

1573, 1580 (Fed. Cir. 1983), and Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392-93 (Fed. Cir. 1988).

Alza maintains that the commercial success of Ditropan XL is a "tribute to the ingenuity" of the '355 patent. Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957 (Fed. Cir. 1997). Mylan, on the other hand, attributes any such success to Alza's marketing and emphasizes that Ditropan XL sales actually fell below Alza's expectations.

It is undisputed that Ditropan XL was a commercial success at launch. (Boghigian Tr. at 1729.) Moreover, the evidence clearly demonstrates that Ditropan XL has enjoyed "significant sales in the relevant market." (See, e.g., DX 2017.) Although marketing efforts influenced Ditropan XL's sales (see DX 2025), Mylan does not prove that the drug's success was contingent on advertising alone. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., 348 F. Supp. 2d 713, 757 (N.D. W. Va. 2004) ("The ultimate success of a prescription [drug] hinges on its clinical properties.") Furthermore, despite yielding a relatively disappointing profit margin, Ditropan XL sales met or exceeded third party analyst projections between 2000 and 2004. (Compare Boghigian Tr. at 1660-66, with DX 1507, at DXL 084960.) Therefore, the Court finds that Ditropan XL was at least a moderate commercial success.

b. Long-Felt and Unsolved Need

A patent's ability to solve a long-felt need before other products do so is a common indicium of nonobviousness. See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 884 (Fed. Cir. 1998). To determine the applicability of this secondary consideration, a court should consider whether "contemporaneous development" met the purported need first. Id. Evidence of the existence of a long-felt need may be found, among other places, in the prior art, Gershon, 372 F.2d at 538, or in the patent itself. Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1366 (Fed. Cir. 2001).

Alza contends that the '355 patent met a long-felt, but unsolved need for sustained relief of urinary incontinence over 24 hours, and with fewer intolerable side effects. Mylan's expert, Dr. Kandzari, agreed that, before Ditropan XL's introduction, there was a need for a once-a-day anticholinergic treatment for urinary incontinence and that Ditropan XL was the first such product. (Kandzari Tr. at 1820.) Moreover, Alza asserts that Ditropan XL's sales demonstrate the existence of such a need. Alza, however, identifies no evidence indicating that the need for a once-a-day urinary incontinence drug was either long-felt or unsolved. To the contrary, the Morella and Baichwal patents substantially (if not completely) solved this need before the filing of the '355 patent.

Therefore, the Court finds that Ditropan XL did not meet a long-felt and unsolved need.

c. Unexpected Results

"[E]vidence of unexpected results may be strong support for a conclusion of nonobviousness." See Lindemann Maschinenfabrik v. Am. Hoist & Derrick, 730 F.2d 1452, 1461 (Fed. Cir. 1984) (citation omitted). Here, Alza argues that the benefits of Ditropan XL were not expected when the '355 patent was filed. According to Alza, it was unexpected that: (1) oxybutynin would be absorbed in the colon in sufficient amounts to provide a therapeutic benefit; (2) colonic absorption of oxybutynin would decrease formation of side effect causing desoxy metabolite; and (3) colonic absorption would produce greater levels of oxybutynin in the blood compared to the immediate release dosage form.

As previously explained, oxybutynin's colonic absorption was reasonably expected by a person of ordinary skill in the art. Likewise, Ditropan XL's decrease in side effects was not surprising. Well before filing for a patent, Alza expected that an OROS oxybutynin product "will reduce the side effects." (DX 1517, at DXL063217.) Its contemporaneous documents confirm that expectation. "The side effects of anticholinergic agents are thought to be peak related. A sustained release OROS-oxybutynin .

. . would be expected to decrease side effects by delivering drugs in a more consistent profile." (PX 308, at DXL063460.)

Other prior art references also suggested that a controlled release version of oxybutynin would reduce side effects. (DX 2009, Tab D at 567; JX 98, at 28.) Thus, although the biochemical means of achieving this result (i.e., decreasing formation of the deoxy metabolite) may have been unexpected, the Court finds that the result itself was not unexpected. (See PX 308 at DXL063460)

Finally, Alza summarily relies on testimony from Dr. Wong and Dr. Peppas to demonstrate the purported unexpectedness of the relatively higher bioavailability of OROS oxybutynin. (See Wong Tr. at 72-73; Peppas Tr. at 256-59.) Although Mylan does not directly rebut this evidence in its briefs, it notes Alza's failure to produce any statistically significant clinical trial data showing that Ditropan XL is more efficacious than IR oxybutynin. (Boghigian Tr. at 1705-11; DX 2011; see also Kandzari Tr. at 1584-90, 1603-04.) Moreover, the Ditropan XL product monograph authored by Dr. Chancellor, one of Alza's experts, states that the "efficacy" of Ditropan XL and IR oxybutynin are "comparable." (PX 157, at 6.) Therefore, insofar as the controlled release oxybutynin formulation produces greater levels of the drug in the blood than the immediate release formulation, Alza fails to establish that the difference is consequential. Accordingly, the

Court finds that any such unexpected result holds nominal persuasive value in the obviousness analysis.

4. Conclusion on Obviousness

Mylan has established a strong prima facie case of obviousness, while Alza's proof of objective indicia of nonobviousness is tenuous. Therefore, after weighing all the evidence on this issue, the Court concludes that Mylan has proven by clear and convincing evidence that the '355 patent is obvious.

IV. CONCLUSION

The Court concludes that Alza has failed to prove that Mylan's accused product infringes the '355 patent. The Court further concludes that the '355 patent was anticipated by the Baichwal and Morella patents and obvious in view of the prior art. Therefore, the Court **DECLARES** that the '355 patent is invalid.

It is so **ORDERED**.

The Clerk shall transmit copies of this Order to counsel of record.

DATED: September 27, 2005.

Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE